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PAPER

Enantioselective synthesis of bio-relevant 3,5-diaryl pyrazolines†

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The straightforward asymmetric construction of bio-relevant Δ^2-pyrazolines having either *N*-(thio)amide or *N*-acetyl functional groups and flanked by aryl substituents such as phenol at C3 and C5 has been achieved through an enantioselective phase transfer organocatalytic addition of *N*-Boc hydrazine to chalcones followed by a transprotection sequence allowing *N*-Boc transformation into *N*-CXNHR (X = S, O) or *N*-Ac functional groups. This approach was applied to a straightforward elaboration of chiral monoamine oxidase inhibitor derivatives.

Introduction

Chiral aza-heterocycle derivatives have been becoming ubiquitous in medicinal chemistry. For instance, architectures derived from the Δ^2-pyrazoline platform have revealed a large array of biological activities with respect to their five-membered ring substitution pattern.[1] Pharmaceutical investigations highlighted several 1,4-dihydropyrazole compounds (Fig. 1) such as **1** and **3–4** as potent monoamine oxidase (MAO) inhibitors. These bioactive derivatives possess a thioamide group (**1**[2] and **3**[3]) or, to a lesser extent, an acetyl functional group (**4**)[4,5] on N1 that is flanked by phenol moieties at C3 and C5 allowing interesting structure–selectivity relationships for subtype MAO-A or MAO-B isoforms.[2–6] In fact, MAO-A inhibitors have been useful for the treatment of psychiatric disorders whereas MAO-B inhibitors were used to treat Parkinson's disease. *N*-Thioamide 3,5-diaryl pyrazoline **2** was also capable of selective inhibition of other type of enzymes such as cyclooxygenase COX-2, an important target for anti-inflammatory drug development.[7] Moreover, the primary thioamide functional group on the pyrazolinyl framework turned out to be a useful building block for the construction of an extra-heterocyclic pendant such as thiazolone **5**, providing a compound possessing anticancer activity.[8,9]

Although it has been shown that enantiopure pyrazolines could lead to more potent or selective ligands for given bio-receptors, these investigations required the use of adapted chiral-HPLC separation[5] or virtual docking based on theoretical calculations for obtaining this information.[10] Furthermore, the absolute configuration of these derivatives has been determined in few cases.[5,11] Unfortunately, the existing diastereoselective,[9] metal-catalyzed,[12] or the more advanced organo-catalyzed enantioselective synthesis of pyrazolines[13] does not allow the elaboration of such 3,5-diaryl pyrazolines featuring a polar group on N1.

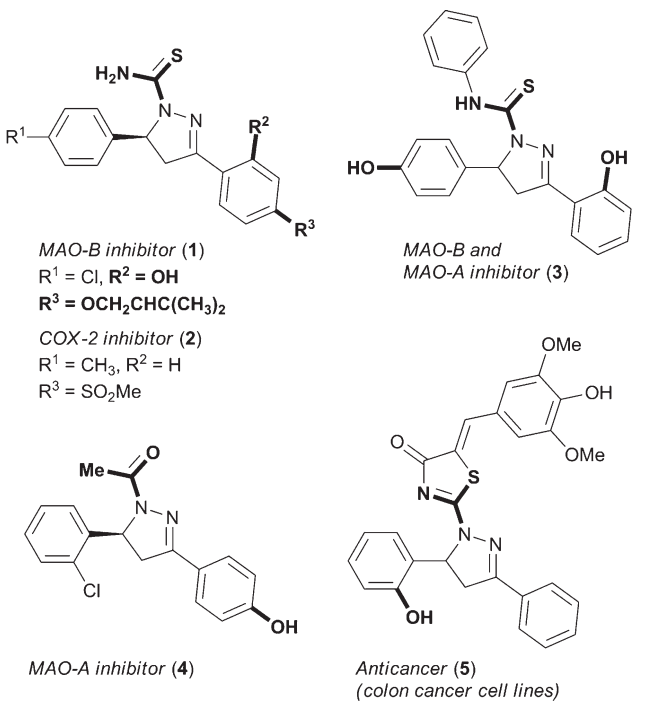

Fig. 1 Bioactive pyrazolines.

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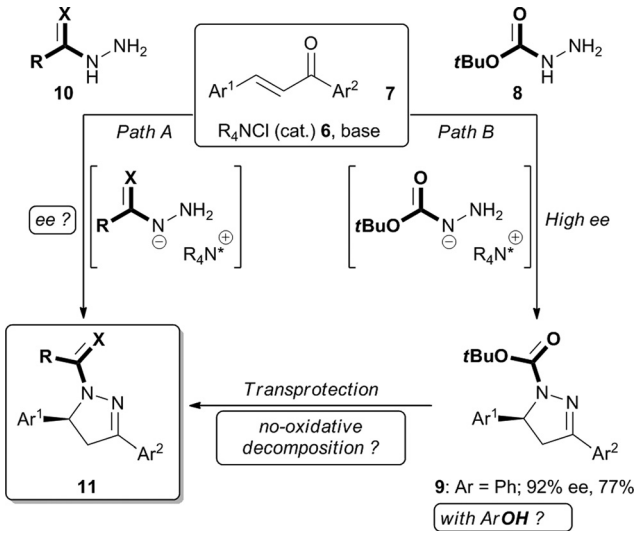


Scheme 1 Synthetic strategy.

To fill the gap, we envisaged the construction of these bio-relevant pyrazolines by exploiting our recently developed enantioselective addition of *N*-Boc hydrazine **8** to chalcones **7** (Scheme 1), through an aza-Michael–cyclocondensation cascade of an hydrazide anion intermediate, under phase transfer organocatalytic (PTC) conditions.[14] The dihydropyrazoles were obtained with high ee, for instance 92% ee and 77% yield from chalcone **7a** ($Ar^1 = Ar^2 = Ph$), but this procedure was limited to the formation of *N*-Boc derivatives such as **9**. Thereby, two novel developments were tackled. First of all, the asymmetric addition of (thio)semicarbazide **10** was investigated (path A) to afford directly the diazoles **11**. Next, we considered a two step sequence (path B) based on the asymmetric addition of *N*-Boc hydrazine **8** followed by innovative transprotection reactions of the obtained *N*-Boc pyrazolines **9** into *N*-thioamides **11** or *N*-acetyl homologues. Either of these strategies will have to be compatible with phenol moieties in order to expect any application towards MAO inhibitors' elaboration.

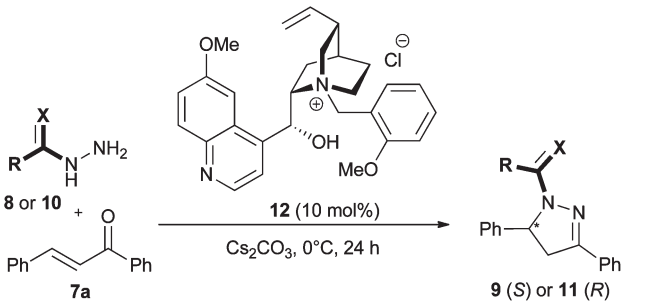
We will disclose hereby the enantioselective synthesis of these type of pyrazolines and an application to the elaboration of MAO-A inhibitor **4** and derivatives as depicted in Fig. 1.

Results and discussion

Synthesis of *N*-(thio)amide pyrazolines by PTC (path A)

We recently discovered the capability of *N*-benzyl quininium salt **12**[15,16] (Table 1) to act as an efficient organocatalyst for the enantioselective synthesis of 3,5-diarylpyrazolines of type **9** from *N*-Boc hydrazine under PTC.[17] Unfortunately, this methodology turned out to be inefficient with *N*-phenyl semicarbazide **10a** (entries 1–2) ruling out the direct asymmetric elaboration of the corresponding pyrazoline **11a** of interest. A mixture of THF and CH_2Cl_2 as solvents was employed to facilitate the solubilisation of the hydrazine component but no improvement was observed (entry 3). Other quininium salts were tested but led also to a strong background reaction. The use of thiosemicarbazide **10b** instead furnished traces of the corresponding diazole **11b** (entry 4). In order to circumvent the limitations of this PTC catalyzed aza-Michael methodology, we developed an improved procedure for the elaboration of *N*-*tert*-butyloxycarbonyl 3,5-diphenyl pyrazoline **9** (entry 5).[14] Accordingly, the dihydropyrazole **9** was easily obtained in virtually enantiopure fashion (>99% ee), without purification on column chromatography, through the asymmetric addition process of *N*-Boc hydrazine **8** to chalcone **7** (4.8 mmol) followed by one recrystallization of the obtained crude product with an overall yield of 53%.

Table 1 Addition of (thio)semicarbazides[a]



Entry	R/X	Solvent	Yield[b] (%)	Ee[c] (%)
1	PhNH/O (**10a**)	Toluene	50 (**11a**)	7
2	PhNH/O (**10a**)	THF	54 (**11a**)[d]	11
3	PhNH/O (**10a**)	THF–CH_2Cl_2	55 (**11a**)	7
4	NH_2/S (**10b**)	THF	5 (**11b**)	nd
5	O*t*Bu/O (**8**)	THF	53 (**9**)[e]	>99

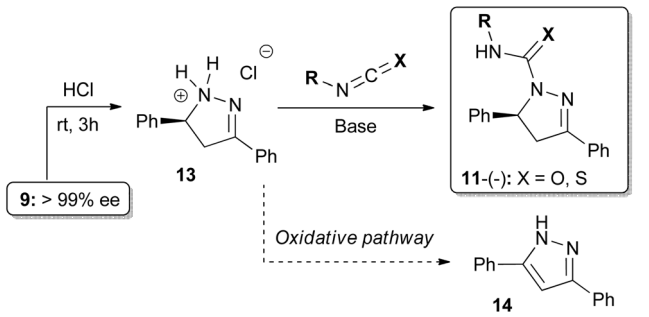
[a] Chalcone **7a** (1 equiv), hydrazine **8** or **10** (1.1 equiv), Cs_2CO_3 (1.3 equiv), ammonium salt **12** (10 mol%) for 24 h at 0 °C. [b] Isolated yield after column chromatography. [c] Determined by chiral HPLC. [d] K_3PO_4 instead of Cs_2CO_3. [e] Yield after one recrystallization.

Enantiopure pyrazoline **9** is thereby ready for the alternative transprotection investigation towards *N*-(thio)amide pyrazolines as depicted in Scheme 1 (path B).

Synthesis of *N*-(thio)amide pyrazolines through a transprotection approach (path B)

Next, we tackled the elaboration of *N*-amide pyrazolines **11** by performing a functional group transformation 'transprotection' of the enantiopure *N*-*tert*-butyloxycarbonyl 3,5-diphenyl pyrazoline **9** in the presence of isocyanate reagents (Table 2). At the outset, we mastered the acidic *N*-Boc deprotection of **9** by means of an excess of HCl in dioxane to afford the 1*H*-pyrazolinium salt **13** *in situ* as a stable ammonium salt. This protonated form prevents the facile oxidation of the corresponding conjugated base 1*H*-pyrazoline into pyrazole **14**. The subsequent one-pot addition of an excess of phenylisocyanate and triethylamine to **13** achieved a smooth transformation into the desired *N*-amide pyrazoline **11a** (entry 1). Despite many efforts, the purification of product **11a** turned out to be unsuccessful, due to the decomposition/oligomerization of the isocyanate reagent. Previously, this strategy was successful to form *N*-acetyl or *N*-sulfonyl pyrazoline derivatives but the extrapolation to *N*-(thio)amide analogues required indeed a complete reinvestigation.[14] Then, we tried the sterically more encumbered Hünig's base in place of

Table 2 Isocyanate transprotection[a]

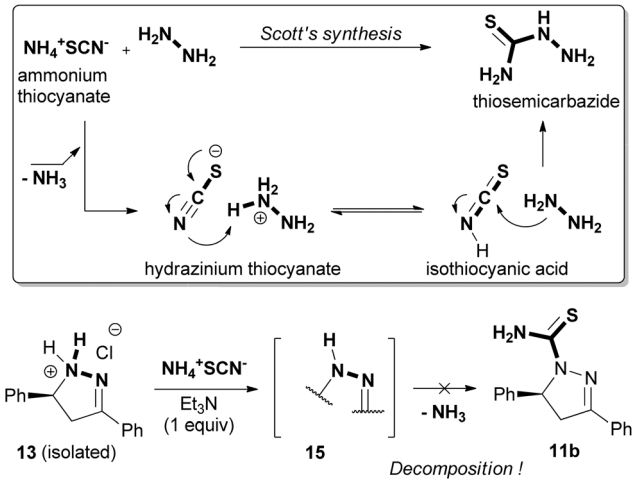


Entry	R	X (equiv)	Base (equiv)	Yield[b] (%)	Ee[c] (%)
1	Ph	O (3.0)	Et_3N (9.0)	98 (**11a**)[d]	nd
2	Ph	O (1.5)	DIEA (9.0)	0 (**11a**)	—
3	Ph	O (1.1)	Et_3N (6.2)	97 (**11a**)	>99
4	Ph	O (1.1)	Et_3N (1.1)	90 (**11a**)[e]	>99
5	$Ph(CH_2)_2$	O (1.1)	Et_3N (6.2)	83 (**11c**)	>99
6	Ph	S (1.1)	Et_3N (6.2)	98 (**11d**)	>99

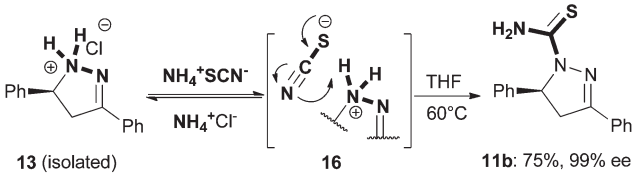
[a] *N*-Boc pyrazoline **9** (1 equiv in CH_2Cl_2), HCl in dioxane (6 equiv, 4 M) for 2 h at rt, then, in one-pot, isocyanate or isothiocyanate and a base at rt, 18 h. [b] Isolated yield after column chromatography. [c] Determined by chiral HPLC. [d] Yield estimated on the ^1H NMR of the crude product by an internal standard. [e] The pyrazolinium salt **13** was isolated by evaporation under vacuum and used subsequently as a crude product.

Et_3N (entry 2) but no pyrazoline **11a** was formed. The formation of pyrazole **14** was observed instead (oxidative pathway) among other unidentified compounds from the ^1H NMR spectrum of the crude product. The activation of isocyanate reagents by tertiary amines acting as a Lewis base so that a faster subsequent nucleophilic addition reaction occurs was already mentioned in the literature.[18] Due to its size, one can assume that *N*,*N*-diisopropylethylamine is a less efficient Lewis base than Et_3N to accelerate the addition step of the 1*H*-pyrazoline derived from **13** over the oxidative decomposition pathway. Eventually, after some optimization, it was found that 1.1 equivalent of phenylisocyanate (*vs.* pyrazoline) and a quasi-stoichiometric amount of Et_3N (*vs.* 6 equiv HCl) afforded the *N*-phenylamide pyrazoline **11a** in 97% isolated yield after an easy column chromatography with up to 99% ee (entry 3). It was also found that the crude pyrazolinium salt **13** could be isolated, without decomposition, after a simple evaporation to remove the excess of solvent and acid. Thereby the subsequent use of only 1.1 equivalent of Et_3N *vs.* pyrazoline (entry 4) in the same pot was allowed. These optimized conditions have been applied to the construction of aliphatic amide **11c** (entry 5) or thioamide **11d** (entry 6) with very good yields without erosion of the enantiomeric excesses.

With the aim of completing this successful enantioselective synthesis of *N*-(thio)amide pyrazolines, we tackled the construction of valuable primary thioamide dihydropyrazoles such as **11b** (Scheme 2). In order to circumvent the use of the sensitive isothiocyanic acid (HNCS) for the transprotection sequence,[19] we made use of the thiosemicarbazide ($NH_2C(S)NHNH_2$) synthesis of Scott *et al.* from a mixture of hydrazine and commercially available ammonium thiocyanate ($NH_4^+SCN^-$) reagent in refluxing water.[20] In this process, a molecule of ammonia is displaced to furnish the corresponding hydrazinium thiocyanate



Scheme 2 Synthesis of *N*-thioamide pyrazoline.



Scheme 3 Synthesis of *N*-thioamide pyrazoline through ion metathesis.

intermediate $NH_2NH_3^+SCN^-$ in equilibrium with a mixture of hydrazine and isothiocyanic acid which undergoes a rearrangement to yield $NH_2C(S)NHNH_2$. We attempted to obtain a similar system (Scheme 2) by generating an equivalent of 1*H*-pyrazoline **15** by mixing the pyrazolinium salt **13** (isolated after evaporation) and 1 equivalent of Et_3N in the presence of $NH_4^+SCN^-$ under different conditions (from rt to 60 °C in water or MeOH), but only traces of the desired product **11b** could be observed along with many side products. This shows that the slow addition step of the moderately reactive isothiocyanic acid leads to side oxidation reaction of the 1*H*-pyrazoline intermediate **15**.

After some trials, we eventually found that a simple mixing between pre-isolated salt **13** and ammonium thiocyanate (3 equiv) gave rise to a smooth formation of *N*-thioamide pyrazoline **11b** in 75% yield and >99% ee (Scheme 3). In that case, a facile counterion exchange took place (ion metathesis process), by liberating a soft acid NH_4Cl,[21] driving the equilibrium toward the formation of intermediate **16** which underwent the rearrangement to construct the C–N bond of **11b**. This *in situ* trapping process prevents the formation of the unstable 1*H*-pyrazoline intermediate **15** in too high concentration.

As matter of fact, the intermediate **16** could also be considered as a mixture of 3,5-diphenyl 1*H*-pyrazoline **15** and thiocyanic acid (HSCN). Therefore, we were curious to see whether a mixture HSCN + NH_4Cl, easily formed *in situ* from an HCl–dioxane solution and NH_4SCN, was sufficiently acidic at 60 °C to achieve the *N*-Boc deprotection followed by the nucleophilic addition of transient 1*H*-pyrazoline **15** to isothiocyanic acid (Scheme 4). Pleasingly, as depicted in Scheme 4, this improved one-pot one-operation procedure furnished the desired pyrazoline

11b with a good 78% yield and >99% ee. Taking into account that the absolute configuration of precursor *N*-Boc 3,5-diaryl pyrazoline **9** is known, this study brings new information regarding the chiral data of the corresponding *N*-(thio)amide pyrazolines of type **11**, for which few details have been given in the literature thus far. Indeed they are all *levo*-(−) isomers in our cases.

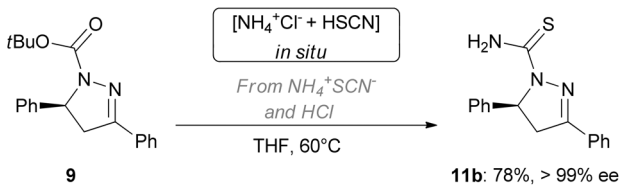
Enantioselective synthesis of MAO-A inhibitor derivatives

Then, we moved to the synthesis of the aforementioned *N*-acetyl pyrazoline **4**, a potent MAO-A inhibitor discovered by Bolasco and co-workers (Scheme 5).[4] We sought to challenge the asymmetric preparation of such a 1,4-dihydropyrazole **4** having both a phenol substituent and an *N*-acetyl functional group (requiring a *N*-Boc transprotection). Besides this objective, compound **4** is one of the rare 3,5-diaryl pyrazolines whose absolute configuration has been determined,[5] which would allow us to validate our model predicting the sense of stereoinduction (quininium derived catalyst **12** giving a *S* pyrazoline).[14] At the outset, it was established that the known chalcone **17**[22] was incompatible with our basic PTC conditions, by precipitating out of the solution. Therefore, the corresponding tetrahydropyran (THP) protected derivative **18** was employed in order to facilitate further acidic deprotection (*vide infra*).[4] Applying the asymmetric aza-Michael–cyclocondensation cascade sequence to this chalcone **18** afforded the pyrazoline **19** with a good 87% yield and high 93% ee for both diastereoisomers resulting from the presence of the THP protecting group. It is noteworthy that this methodology was affected neither by the ring substituents at the *ortho* or *para* position, nor by the sterically encumbered and chiral OTHP protecting group. Then, a smooth one-pot *N*-Boc and OTHP deprotection was orchestrated upon acidic conditions to furnish diazole **20** after an *in situ* di-acetylation reaction. Eventually, a selective acetyl deprotection of the phenol moiety was performed to give rise to the formation of the bio-relevant pyrazoline **4** with no racemization (93% ee). Compound **4** featured the *S* absolute configuration with respect to the analytical Cirilli *et al.*'s studies on HPLC and optical rotation.[5] This outcome corroborates our asymmetric model besides providing, overall, a straightforward enantioselective synthesis of such bioactive pyrazolines.

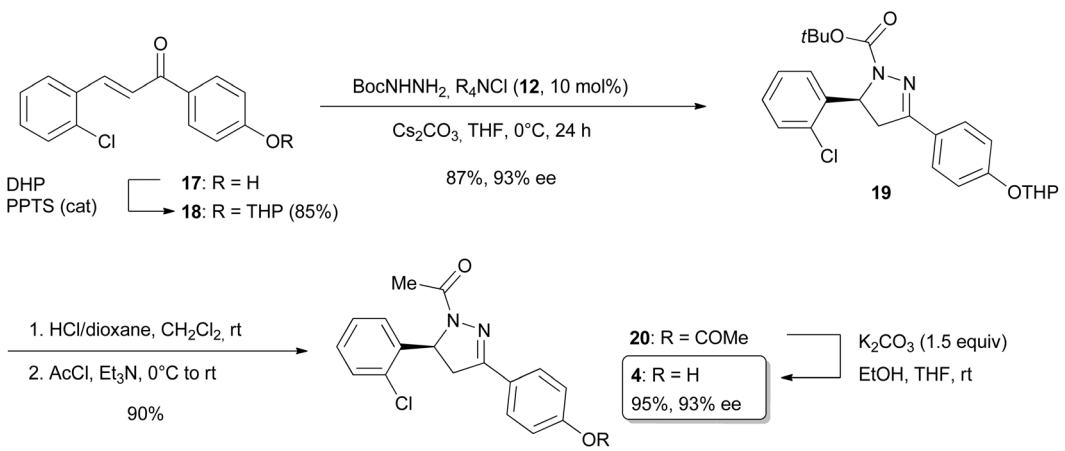
At this stage it was appealing to test our *N*-Boc to *N*-$CSNH_2$ transprotection from the more elaborated *N*-Boc pyrazoline **19** in order to provide **22** (Scheme 6). However, whether the two step (see Scheme 3) or the one-pot procedure (see Scheme 4) was carried out, we were not able to purify the obtained compound **22** due to side products formation, although the ^{1}H NMR spectrum of the crude product revealed a complete conversion into **22**. Thus we undertook to remove firstly and selectively the THP protective group by means of the soft pyridinium *para*-toluenesulfonate acid to give phenol **21** which was used further without purification. To our delight, despite the poor solubility of **21**, the one-pot transprotection conditions turned out to be successful, chemoselective and non-racemising to furnish the *N*-thioamide pyrazoline **22** with 53% yield over three chemical steps from **19**. Therefore, this procedure provides MAO inhibitor derivatives such as **22** displaying further chemical diversity on N1.

Conclusions

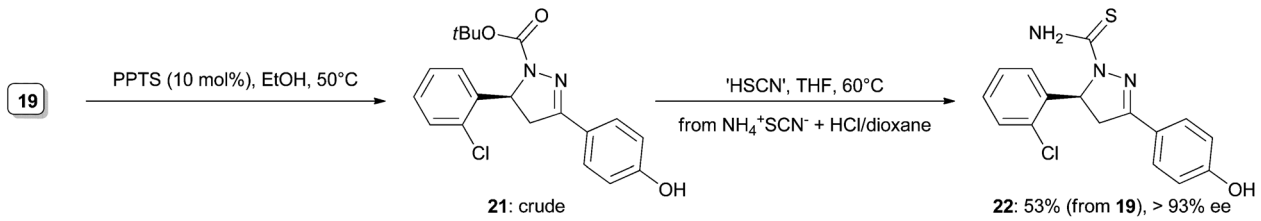
In conclusion, we have shown that an enantioselective addition of *N*-Boc hydrazine to chalcones under organocatalytic PTC conditions followed by a one-pot *N*-Boc transprotection is a competent and practical synthetic sequence for the construction of bio-relevant pyrazolines having phenol substituent at C3 and C5 and *N*-(thio)amide or *N*-acetyl pendant on N1, as illustrated by the enantioselective construction of MAO inhibitor derivatives. Moreover, these data bring useful information concerning the absolute configuration of this family of pyrazolines for which only a handful data are provided in literature.



Scheme 4 One-pot one-step process to *N*-thioamide pyrazoline.



Scheme 5 First enantioselective synthesis of the MAO-A inhibitor **4**.



Scheme 6 Enantioselective synthesis of MAO inhibitor derivatives.

Experimental

General

Chromatographic purification of compounds was achieved with 60 silica gel (40–63 μm). Thin layer chromatography was carried out on silica gel 60 F_{254} (1.1 mm) with spot detection under UV light or phosphomolybdic acid or $KMnO_4$ oxidation. ^1H NMR spectra were recorded at 300 MHz on a Bruker AVANCE 300. Data appear in the following order: chemical shifts in ppm, number of protons, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant J in Hz. ^{13}C NMR spectra were acquired at 75.4 MHz operating with broad band ^1H decoupling. The hydrogen multiplicity was obtained by DEPT135 or Attached Proton Test (APT) using JMOD pulse program. IR spectra were recorded on a Perkin Elmer IRTF 1650 spectrometer with solid dispersed on KBr pastille. Mp's stand uncorrected. HPLC analyses were performed with Daicel Chiralpack® columns (4.6 mm × 25 cm) and a mixture of heptane–isopropanol solvents. A spectrosystem UV detector and a chiral detector (polarimeter) were used. Optical rotations were measured at 20 °C in $CHCl_3$ with a micropolarimeter. Racemic samples as references were prepared by means of either previous methodologies[23] or using *n*-tetrabutylammonium bromide instead of chiral cinchona alkaloids. 3,5-Diphenyl pyrazole **14** and pyrazolinium salt **13** are known compounds.[14,24]

***tert*-Butyl 3,5-diphenyl-4,5-dihydro-1*H*-pyrazole-1-carboxylate (9).** This is an improved procedure on a bigger scale of the previously reported enantioselective synthesis of this pyrazoline which prevented the use of any purification on column chromatography.[14] *trans*-Benzylidenacetophenone **7a** (Ar^1 = Ar^2 = H, 1 g, 4.8 mmol), *tert*-butyl carbazate **8** (712 mg, 5.4 mmol, 1.1 equiv), *N*-2-methoxybenzyl quininium chloride **12** (231 mg, 0.48 mmol, 0.1 equiv) and caesium carbonate (2 g, 6.24 mmol, 1.3 equiv) were introduced into a Schlenk flask. Anhydrous THF (9 mL) was added under nitrogen atmosphere and a vigorous stirring was achieved for 24 h at 0 °C. Then, AcOEt (5 mL) and a saturated aqueous solution of ammonium chloride (5 mL) were poured into the reaction mixture. The phases were separated and the organic layer was washed with water and brine. After evaporation of the solvent under vacuum, the crude residue was dissolved in a small volume of dichloromethane and passed through a plug of silica gel (AcOEt). After evaporation of the solvent under vacuum, the solid was recrystallized in a refluxing solution of AcOEt–petroleum ether (1 : 3, 40 mL) to give 823 mg (53%, ee >99%) of the enantioenriched *N*-Boc pyrazoline **9**. Anal. calcd for $C_{20}H_{22}N_2O_2$ (322.40): C, 74.51; H, 6.88; N, 8.69. Found: C, 74.50; H; 6.67; N, 8.80. The analytical data match the previously reported ones.[14]

Representative procedure for the synthesis of *N*-3,5-triphenyl-4,5-dihydro-1*H*-pyrazole-1-carboxamide (11a). To a solution of enantioenriched *tert*-butyl 3,5-diphenyl-4,5-dihydro-1*H*-pyrazole-1-carboxylate **9** (40 mg, 0.124 mmol, >99% ee) in anhydrous CH_2Cl_2 (0.5 mL) at 0 °C under nitrogen atmosphere was added dropwise a HCl–dioxane 4 M solution (186 μL, 0.744 mmol, 6 equiv). The reaction mixture was stirred at room temperature for 3 h. Phenyl isocyanate (14.9 μL, 0.137 mmol, 1.1 equiv) and, subsequently, triethylamine (107.2 μL, 0.769 mmol, 6.2 equiv) were added dropwise at 0 °C. The mixture was vigorously stirred at room temperature for 18 hours. An HCl aqueous solution (0.5 M) was poured into the flask. The aqueous phase was extracted with CH_2Cl_2 and the combined organic layers were washed with a NaOH aqueous solution (0.25 M), brine and dried over Na_2SO_4. After filtration, the solvent was removed under vacuum and the residue was purified by column chromatography on silica gel (dichloromethane, R_f = 0.32) to give the enantioenriched *N*-phenylamide pyrazoline **11a** in 97% yield (41 mg, >99% ee) as a white powder. m.p. = 140–142 °C (litt.[23] 164–166 °C for a racemic). $[\alpha]_D^{20} = -132°$ $cm^3\ g^{-1}\ dm^{-1}$ (c = 0.0054 g cm^{-3} in $CHCl_3$). HRMS *m*/*z* calcd for $C_{22}H_{20}N_3O$ [M + H]+: 342.1606, found: 342.1592. The NMR analytical data match the previously reported NMR analyses.[23] HPLC using a Chiralpack IA Daicel chiral column, iPrOH–heptane (50 : 50) eluent at a flow rate of 1 mL min^{-1} at 20 °C, λ = 230 nm. The major enantiomer eluted at 24.9 min (the *levo* (−) isomer) and the minor enantiomer at 9.1 min (the *dextro* (+) isomer) giving >99% ee.

Two step procedure: To a solution of enantioenriched (>99% ee) *tert*-butyl 3,5-diphenyl-4,5-dihydro-1*H*-pyrazole-1-carboxylate **9** (40 mg, 0.124 mmol) in anhydrous CH_2Cl_2 (0.5 mL) at 0 °C under nitrogen atmosphere was added dropwise a HCl–dioxane 4 M solution (186 μL, 6 equiv). The reaction mixture was stirred at room temperature for 3 h. Then solvents were evaporated and the crude residue was dissolved in dichloromethane (0.5 mL). Phenyl isocyanate (14.9 μL, 0.137 mmol, 1.1 equiv) and, subsequently, triethylamine (20.7 μL, 0.148 mmol, 1.2 equiv) were added dropwise at 0 °C. The mixture was vigorously stirred at room temperature for 18 hours. An HCl aqueous solution (0.5 M) was poured into the flask. The aqueous phase was extracted with CH_2Cl_2 and the combined organic layers were washed with a NaOH aqueous solution (0.25 M), brine and dried over Na_2SO_4. After filtration, the solvent was removed under vacuum and the residue was purified by column chromatography on silica gel (dichloromethane, R_f = 0.32) to give the

enantiopure *N*-phenylamide pyrazoline **11a** (38 mg, >99% ee) in 90% yield.

N*-Phenethyl-3,5-diphenyl-4,5-dihydro-1*H*-pyrazole-1-carboxamide (11c).** *Prepared from phenethylisocyanate according to the procedure used for compound **11a. **11c** was obtained as an enantioenriched mixture (38 mg, >99% ee) in 83% yield after purification by two column chromatographies on silica gel (R_f = 0.23 – petroleum ether–EtOAc: 7 : 3, 0.62 – dichloromethane–diethyl ether: 9 : 1). White solid, m.p. = 114–116 °C. $[\alpha]_D^{20}$ = −72° cm^3 g^{-1} dm^{-1} (c = 0.00575 g cm^{-3} in $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.78–2.96 (m, 2H), 3.16 (dd, J = 17.6, J = 5.8 Hz, 1H), 3.43–3.65 (m, 2H), 3.77 (dd, J = 17.6, J = 12.1 Hz, 1H), 5.52 (dd, J = 12.1, J = 5.7 Hz, 1H), 6.12–6.25 (m, 1H), 7.19–7.38 (m, 10H), 7.38–7.46 (m, 3H), 7.61–7.70 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 36.8 (CH2), 41.5 (CH2), 42.9 (CH2), 60.7 (CH), 125.7 (CH), 126.4 (CH), 126.5 (CH), 127.7 (CH), 128.6 (CH), 128.8 (CH), 129.0 (CH), 129.1 (CH), 130.2 (CH), 131.6 (C), 139.4 (C), 143.0 (C), 151.0 (C), 154.7 (C). IR (ATR) ν (cm^{-1}): 3416, 2927, 1675, 1518, 1383, 700, 689. HRMS *m*/*z* calcd for $C_{24}H_{24}N_3O$ $[M + H]^+$: 370.1919, found: 370.1904. HPLC using a Chiralpack IA Daicel chiral column, iPrOH–heptane (20 : 80) eluent at a flow rate of 0.8 mL min^{-1} at 20 °C, λ = 230 nm. The major enantiomer eluted at 21.1 min (the *levo* (−) isomer) and the minor enantiomer at 15.4 min (the *dextro* (+) isomer) giving >99% ee.

N*-3,5-Triphenyl-4,5-dihydro-1*H*-pyrazole-1-carbothioamide (11d).** *Prepared from phenyl thioisocyanate according to the procedure used for compound **11a. **11d** was obtained as an enantioenriched mixture (44 mg, >99% ee) in 98% yield, after purification by column chromatography on silica gel (R_f = 0.75 – dichloromethane). White solid, m.p. = 205–207 °C (litt.[25] 105 °C for a racemic). $[\alpha]_D^{20}$ = −266° cm^3 g^{-1} dm^{-1} (c = 0.00555 g cm^{-3} in $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.25 (dd, J = 17.7, J = 3.7 Hz, 1H), 3.88 (dd, J = 17.7, J = 11.6 Hz, 1H), 6.20 (dd, J = 11.6, J = 3.7 Hz, 1H), 7.14–7.22 (m, 1H), 7.23–7.40 (m, 7H), 7.41–7.51 (m, 3H), 7.62–7.69 (m, 2H), 7.74–7.82 (m, 2H), 9.29 (brs, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 42.8 (CH2), 63.4 (CH), 124.4 (CH), 125.6 (CH), 125.6 (CH), 127.0 (CH), 127.7 (CH), 128.7 (CH), 129.0 (CH), 129.0 (CH), 130.8 (C), 131.0 (CH), 138.8 (C), 142.1 (C), 155.2 (C), 174.1 (C). IR (ATR) ν (cm^{-1}): 3337, 1512, 1444, 1400, 1324, 754, 690, 534. HRMS *m*/*z* calcd for $C_{22}H_{20}N_3S$ $[M + H]^+$: 358.1378, found: 358.1361. HPLC using a Chiralpack IA Daicel chiral column, iPrOH–heptane (40 : 60) eluent at a flow rate of 1 mL min^{-1} at 20 °C, λ = 230 nm. The major enantiomer eluted at 10.4 min (the *levo* (−) isomer) and the minor enantiomer at 18.8 min (the *dextro* (+) isomer) giving >99% ee.

3,5-Diphenyl-4,5-dihydro-1*H*-pyrazole-1-carbothioamide (11b). *One-pot two step procedure* (Scheme 3). To a solution of enantiopure *tert*-butyl 3,5-diphenyl-4,5-dihydro-1*H*-pyrazole-1-carboxylate **9** (40 mg, 0.124 mmol, 99% ee) in anhydrous CH_2Cl_2 (0.5 mL) at 0 °C under nitrogen atmosphere was added dropwise a HCl–dioxane 4 M solution (186 µL, 0.744 mmol, 6 equiv). The reaction mixture was stirred at room temperature for 2 h. After evaporation of solvents, ammonium thiocyanate (28.3 mg, 0.372 mmol, 3 equiv) was added under nitrogen followed by degassed anhydrous THF (0.6 mL). Tube was sealed and the mixture was vigorously stirred at 60 °C temperature for 72 hours. At the end of the reaction, the solvent was removed under vacuum. The residue was dissolved in AcOEt (5 mL), washed 2 times with water, brine, and dried over Na_2SO_4. After filtration, the solvent was removed under vacuum and the residue was purified by column chromatography on silica gel (dichloromethane, R_f = 0.39) to give the enantiopure pyrazoline **11b** in 75% (26 mg, >99% ee) yield as yellow solid. m.p. = 183–185 °C (litt.[23] 196–199 °C for a racemic). $[\alpha]_D^{20}$ = −275° cm^3 g^{-1} dm^{-1} (c = 0.0051 g cm^{-3} in $CHCl_3$). HRMS *m*/*z* calcd for $C_{16}H_{16}N_3S$ $[M + H]^+$: 282.1065, found: 282.1062. The NMR analytical data matched the previously reported NMR analyses.[23] HPLC using a Chiralpack IA Daicel chiral column, iPrOH–heptane (50 : 50) eluent at a flow rate of 1 mL min^{-1} at 20 °C, λ = 230 nm. The major enantiomer eluted at 7.7 min (the *levo* (−) isomer) and the minor enantiomer at 11.2 min (the *dextro* (+) isomer) giving >99% ee.

One-pot one-step procedure (Scheme 4). Ammonium thiocyanate (118 mg, 1.55 mmol, 10 equiv) was dissolved in anhydrous degassed THF (0.6 mL) in a tube under nitrogen. Hydrochloric acid (4 N solution in dioxane, 387.7 µL, 1.55 mmol, 10 equiv) was added dropwise, forming a pink precipitate which instantaneously turned to white at the end of addition. The mixture was stirred at room temperature for 10 min and *tert*-butyl 3,5-diphenyl-4,5-dihydro-1*H*-pyrazole-1-carboxylate **9** (50 mg, 0.155 mmol, 1 equiv, 99% ee) was poured into the solution. Then, the tube was sealed and heated at 60 °C for 30 hours with vigorous stirring. After evaporation of solvent under vacuum, dichloromethane (5 mL) and water (5 mL) was added, and the aqueous phase was neutralized till pH 7 with an aqueous NaOH solution (1 M) added dropwise. Then the mixture was extracted with dichloromethane and the combined organic phases were washed with brine, dried over Na_2SO_4 and evaporated under vacuum after filtration. The residue was purified by column chromatography on silica gel (dichloromethane, R_f = 0.39) to give the enantiopure pyrazoline **11b** (34 mg, >99% ee) in 78% yield as a yellow solid.

(*E*)-3-(2-Chlorophenyl)-1-(4-(tetrahydro-2*H*-pyran-2-yloxy)-phenyl)prop-2-enone (18). Chalcone **17** (150 mg, 0.58 mmol) and pyridinium *p*-toluenesulfonate (3.5 mg, 0.014 mmol, 0.024 equiv) were stirred under nitrogen in anhydrous dichloromethane (3 mL) at room temperature for 15 min. Then dihydropyran (225 µL, 2.4 mmol, 4.2 equiv) was added dropwise and the reaction mixture was vigorously stirred at room temperature until the total disappearance of the starting chalcone (checked by NMR) *i.e.* 24 hours. After evaporation of solvent under vacuum, the crude yellow oil was dissolved in diethyl ether (5 mL) and the solution was washed 5 times with water, then brine and finally dried over $MgSO_4$. After filtration, the solvent was removed under vacuum. The obtained yellow oil was ground in pentane with a spatula giving a solid which was isolated by filtration and washed with pentane. Chalcone **18** was obtained as a pale yellow powder in 85% yield (171 mg). m.p. = 81–83 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.59–1.79 (m, 3H), 1.86–1.93 (m, 2H), 1.95–2.09 (m, 1H), 3.59–3.69 (m, 1H), 3.80–3.93 (m, 1H), 7.10–7.18 (m, 2H), 7.27–7.37 (m, 2H), 7.39–7.46 (m, 1H), 7.49 (d, J = 15.7 Hz, 1H), 7.70–7.79 (m, 1H), 7.97–8.06 (m, 2H), 8.16 (d, J = 15.7 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 18.6

(CH2), 25.1 (CH2), 30.2 (CH2), 62.1 (CH2), 96.2 (CH), 116.2 (CH), 124.8 (CH), 127.1 (CH), 127.8 (CH), 130.3 (CH), 130.9 (CH), 131.0 (CH), 131.5 (C), 133.5 (C), 135.5 (C), 139.8 (CH), 161.2 (C), 188.8 (C). IR (KBr) ν (cm^{-1}) 2940, 1654, 1606, 1508, 1334, 1242, 1177, 1114, 1022, 952, 917, 762. HRMS *m/z* calcd for $C_{20}H_{20}O_3Cl$ $[M + H]^+$: 343.1101, found: 343.1114. *Remark*: this product is unstable and should be stored under nitrogen at −20 °C.

***tert*-Butyl-3-(4-(tetrahydropyran-2-yloxy)phenyl)-5-(2-chlorophenyl)-4,5-dihydro-1*H*-pyrazole-1-carboxylate (19).** Chalcone **18** (117.3 mg, 0.342 mmol), *tert*-butyl carbazate **8** (98%, 50.8 mg, 0.376 mmol, 1.1 equiv), *N*-2-methoxybenzyl quininium chloride **12** (16.4 mg, 0.034 mmol, 0.1 equiv) and caesium carbonate (145 mg, 0.445 mmol, 1.3 equiv) were introduced in a Schlenk flask. Anhydrous THF (1 mL) was added under nitrogen atmosphere and a vigorous stirring was achieved for 24 h at 0 °C. Then, AcOEt (3 mL) was poured into the reaction mixture and caesium carbonate was removed by filtration. The filtrate was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel (petroleum ether–EtOAc = 4 : 1, R_f = 0.24) to afford *tert*-butyl-3-(4-(tetrahydropyran-2-yloxy)phenyl)-5-(2-chlorophenyl)-4,5dihydro-1*H*-pyrazole-1-carboxylate **19** as a white powder (136 mg, 87% yield, 93% ee). m.p. = 79–81 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33 (brs, 9H), 1.58–1.76 (m, 3H), 1.80–1.90 (m, 2H), 1.91–2.08 (m, 1H), 3.02 (dd, J = 17.5; 5.1 Hz, 1H), 3.53–3.66 (m, 1H), 3.80 (dd, J = 17.6; 12.2 Hz, 1H), 3.81–3.92 (m, 1H), 5.42–5.49 (m, 1H), 5.76 (dd, J = 12.0; 5.3 Hz, 1H), 6.99–7.08 (m, 2H), 7.16–7.24 (m, 3H), 7.33–7.40 (m, 1H), 7.64–7.73 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 18.7 (CH_2), 25.2 (CH_2), 28.2 (CH_3), 30.3 (CH_2), 41.8 (CH_2), 58.8 (CH), 62.1 (CH_2), 81.3 (C), 96.3 (CH), 116.4 (CH), 116.5 (CH), 125.0 (C), 126.3 (C), 127.5 (CH), 128.3 (CH), 128.7 (CH), 129.7 (CH), 131.6 (C), 151.8 (C), 152.6 (C), 158.7 (C). IR (KBr) ν (cm^{-1}) 2941, 2868, 1724, 1696, 1607, 1395, 1242, 1147, 1123, 1037, 960, 920. HRMS *m/z* calcd for $C_{25}H_{30}N_2O_4Cl$ $[M + H]^+$: 457.1894, found: 457.1892. HPLC using a Chiralpack AD-H Daicel chiral column, iPrOH–heptane (20 : 80) eluent at a flow rate of 1 mL min^{-1} at 20 °C, λ = 298 nm. HPLC using a Chiralpack AD-H Daicel chiral column, iPrOH–heptane (20 : 80) eluent at a flow rate of 1 mL min^{-1} at 20 °C, λ = 298 nm. The major *S* enantiomer (with respect to the absolute configuration of C5 of the pyrazoline ring, the *levo* (−) isomer) eluted at 12.9 min and 15.3 min (two peaks because of THP protecting group) and the minor enantiomer at 31.5 min and 38.5 min (the *dextro* (+) isomer) giving 93% ee.

1-Acetyl-3-(4-acetoxyphenyl)-5-(2-chlorophenyl)-4,5-dihydro-1*H*-pyrazole (20)

To a solution of enantioenriched *tert*-butyl-3-(4-(tetrahydropyran-2-yloxy)phenyl)-5-(2-chlorophenyl)-4,5dihydro-1*H*-pyrazole-1-carboxylate **19** (100 mg, 0.219 mmol) in anhydrous CH_2Cl_2 (0.9 mL) at 0 °C under nitrogen atmosphere was added dropwise a HCl–dioxane 4 M solution (436 µL, 8 equiv). The reaction mixture was stirred at room temperature for 2 h. Acetyl chloride (62 µL, 0.872 mmol, 4 equiv) and, subsequently, triethylamine (395 µL, 2.83 mmol, 13 equiv) were added dropwise at 0 °C. The mixture was vigorously stirred at room temperature for 2 hours. An HCl aqueous solution (0.5 M) was poured into the flask. The aqueous phase was extracted with CH_2Cl_2 and the combined organic layers were washed with brine and dried over $MgSO_4$. After filtration, the solvent was removed under vacuum and the residue was purified by column chromatography on silica gel (petroleum ether–EtOAc = 3 : 2, R_f = 0.31) to give the diacetylated pyrazoline **20** in 90% yield (67 mg) as an off-white solid. m.p. = 162–164 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.30 (s, 3H), 2.48 (s, 3H), 3.04 (dd, J = 17.7; 4.9 Hz, 1H), 3.83 (dd, J = 17.7; 11.9 Hz, 1H), 5.92 (dd, J = 11.9; 4.8 Hz, 1H), 6.99–7.08 (m, 1H), 7.10–7.17 (m, 2H), 7.17–7.24 (m, 2H), 7.36–7.43 (m, 1H), 7.70–7.79 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.2 (CH_3), 22.0 (CH_3), 41.6 (CH_2), 57.9 (CH), 122.1 (CH), 126.0 (CH), 127.4 (CH), 127.9 (CH), 128.9 (CH), 129.1 (C), 130.2 (CH), 131.8 (C), 138.5 (C), 152.3 (C), 153.5 (C), 169.0 (C), 169.2 (C). IR (KBr) ν (cm^{-1}) 2922, 1755, 1655, 1424, 1361, 1191, 911, 763. HRMS *m/z* calcd for $C_{19}H_{18}N_2O_3Cl$ [M + H]+: 357.1006, found: 357.1007.

1-Acetyl-3-(4-hydroxyphenyl)-5-(2-chlorophenyl)-4,5-dihydro-1*H*-pyrazole (4). The diacetylated pyrazoline **20** (58 mg, 0.162 mmol, 1 equiv) and potassium carbonate (34 mg, 0.246 mmol, 1.5 equiv) were stirred in a ethanol–THF (2.6 mL : 2.6 mL) mixture for 16 hours. Then the solvents were evaporated under vacuum and dichloromethane (5 mL) with a few drops of methanol were added to the residue. After addition of a 0.5 M HCl solution, the aqueous phase was extracted with dichloromethane. The organic phase was washed with brine, dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by column chromatography on silica gel (petroleum ether–EtOAc = 3 : 2, R_f = 0.25) to give the enantioenriched 1-acetyl-3-(4-hydroxyphenyl)-5-(2-chlorophenyl)-4,5-dihydro-1*H*-pyrazole **4** as a white powder (49 mg, 95%, 93% ee). m.p. = 194–196 °C (litt.[4] 214–215 °C for a racemic). ^{1}H NMR (300 MHz, MeOD) δ 2.43 (s, 3H), 3.02 (dd, J = 17.8; 4.7 Hz, 1H), 3.91 (dd, J = 17.8; 11.7 Hz, 1H), 5.87 (dd, J = 11.6; 4.6 Hz, 1H), 6.77–6.87 (m, 2H), 7.02–7.12 (m, 1H), 7.21–7.31 (m, 2H), 7.40–7.47 (m, 1H), 7.60–7.68 (m, 2H). ^{13}C NMR (MeOD, 75 MHz) δ 21.8 (CH_3), 42.6 (CH_2), 58.9 (CH), 116.6 (CH), 123.6 (C), 127.1 (CH), 128.5 (CH), 129.7 (CH), 130.0 (CH), 131.0 (CH), 132.8 (C), 140.1 (C), 157.3 (C), 161.3 (C), 170.6 (C). IR (KBr) ν (cm^{-1}) 2927, 1593, 1473, 1440, 1364, 1287, 1238, 1173, 836, 755. HRMS *m/z* calcd for $C_{17}H_{16}N_2O_2Cl$ [M + H]+: 315.0900, found: 315.0907. HPLC using a Chiralpack OJ-H Daicel chiral column, iPrOH–heptane (20 : 80) eluent at a flow rate of 1 mL min^{-1} at 20 °C, λ = 298 nm. The minor enantiomer eluted at 20.7 min (the *dextro* (+)-*R* isomer) and the major enantiomer at 33.5 min (the *levo* (−)-*S* isomer) giving 93% ee; or HPLC using a Chiralpack AD-H Daicel chiral column, iPrOH–heptane (20 : 80) eluent at a flow rate of 1 mL min^{-1} at 20 °C, λ = 298 nm. The minor enantiomer eluted at 26.3 min (the *dextro* (+)-*R* isomer) and the major enantiomer at 35.0 min (the *levo* (−)-*S* isomer) giving 93% ee. Absolute configurations were determined in accordance with literature data.[5]

***tert*-Butyl 5-(2-chlorophenyl)-3-(4-hydroxyphenyl)-4,5-dihydro-1*H*-pyrazole-1-carboxylate (21).** *tert*-Butyl-3-(4-(tetrahydropyran-

2-yloxy)phenyl)-5-(2-chlorophenyl)-4,5dihydro-1*H*-pyrazole-1-carboxylate **19** (50 mg, 0.109 mmol) and pyridinium *p*-toluenesulfonate (3 mg, 0.012 mmol, 0.1 equiv) were stirred overnight (18 h) in EtOH (0.9 mL) at 55 °C. The obtained white precipitate was isolated by filtration, washed with cold ethanol, pentane, and was used for the next step without further purification. ^{1}H NMR (300 MHz, DMSO) δ 1.23 (s, 9H), 2.94–3.00 (m, 1H, broad dd), 3.84 (dd, J = 17.6; 12.0 Hz, 1H), 5.62 (dd, J = 11.9; 5.1 Hz, 1H), 6.78–6.81 (m, 2H), 7.06–7.11 (m, 1H), 7.27–7.36 (m, 2H), 7.46–7.50 (m, 1H), 7.53–7.56 (m, 2H). ^{13}C NMR (DMSO, 75 MHz) δ 27.8 (CH_3), 41.1 (CH_2), 58.3 (CH), 79.9 (C), 115.5 (CH), 122.2 (C), 126.3 (C, broad signal), 127.8 (CH), 128.3 (CH), 129.0 (CH), 129.5 (CH), 130.8 (C), 140.3 (C, broad signal), 152.8 (C), 159.3 (C). Two CH are overlaps. MS (ESI) [M + Na]+: 395.1.

5-(2-Chlorophenyl)-3-(4-hydroxyphenyl)-4,5-dihydro-1*H*-pyrazole-1-carbothioamide (22). Ammonium thiocyanate (64.3 mg, 0.845 mmol, 10 equiv) was dissolved in anhydrous degassed THF (0.6 mL) in a tube under nitrogen. Hydrochloric acid (4 N solution in dioxane, 212 µL, 1.55 mmol, 10 equiv) was added dropwise, forming a pink precipitate which instantaneously turned into a white precipitate at the end of the addition. The mixture was stirred at room temperature for 10 min and enantioenriched 5-(2-chlorophenyl)-3-(4-hydroxyphenyl)-4,5-dihydro-1*H*-pyrazole-1-carboxylate **21** (31.5 mg, 0.0845 mmol, 1 equiv, 93% ee) was poured into the solution. Then, the tube was sealed and heated at 60 °C for 72 hours under vigorous stirring. After evaporation of solvent under vacuum, ethyl acetate (5 mL) was added. The solution was washed with water till neutral pH was reached, then it was washed with an aqueous $NaHCO_3$ solution (10% m/m) and brine. It was finally dried over Na_2SO_4 and evaporated under vacuum after filtration. The residue was purified by column chromatography on silica gel (petroleum ether–EtOAc = 2 : 3, R_f = 0.22) to give the enantioenriched pyrazoline **22** (19.2 mg, 53% from product **19**, 93% ee) as a yellow solid. m.p. = 125–127 °C. ^{1}H NMR (300 MHz, MeOD) δ ^{1}H NMR (300 MHz, MeOD) δ 3.03 (dd, J = 17.8, 3.7 Hz, 1H), 3.93 (dd, J = 17.8, 11.4 Hz, 1H), 6.26 (dd, J = 11.3, 3.7 Hz, 1H), 6.98–7.06 (m, 1H), 6.78–6.85 (m, 2H), 7.38–7.45 (m, 1H), 7.19–7.26 (m, 2H), 7.63–7.71 (m, 2H). ^{13}C NMR (MeOD, 75 MHz) δ 42.8 (CH_2), 62.4 (CH), 116.6 (CH), 123.3 (C), 127.1 (CH), 128.4 (CH), 129.7 (CH), 130.1 (CH), 130.8 (CH), 132.4 (C), 141.0 (C), 158.0 (C), 161.6 (C), 177.4 (C). IR (KBr) ν (cm^{-1}) 3435, 1605, 1470, 1331, 1170, 830, 758. HRMS m/z calcd for $C_{16}H_{15}ClN_3OS$ [M + H]+: 332.0624, found: 332.0622. HPLC using a Chiralpack IA Daicel chiral column, iPrOH–heptane (50 : 50) eluent at a flow rate of 1 mL min^{-1} at 20 °C, λ = 254 nm. The major enantiomer eluted at 5.4 min (the *levo* (−) isomer) and the minor enantiomer at 7.1 min (the *dextro* (+) isomer) giving >93% ee. *Remark*: this powder featured various solubility properties with respect to different batches, likely due to polymorphism issues. The addition of methanol was often required to solubilize the solid.

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